UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/862,798	05/22/2001	Tammy L. Moser	05882.0101.CPUS01	1167

27194 7590 12/08/2004

HOWREY SIMON ARNOLD & WHITE, LLP
C/O M.P. DROSOS, DIRECTOR OF IP ADMINISTRATION
2941 FAIRVIEW PK
BOX 7
FALLS CHURCH, VA 22042

EXAMINER	
HUFF, SHEELA JITENDRA	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/862,798	MOSER ET AL.	
	Examiner	Art Unit	
	Sheela J Huff	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *3,8,10,13,18,23,28 and 31-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,9,11,12,14-17,19-22,24-27,29,30 and 48-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-2, 4-7, 9, 11-12, 14-17, 19-22, 24-27, 29-30 and 48-52, as they read on antibodies and fragments thereof, in the reply filed on 9/30/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-2, 4-7, 9, 11-12, 14-17, 19-22, 24-27, 29-30 and 48-52, as they read on antibodies and fragments thereof, are currently under consideration.

Claims 3, 8, 10, 13, 18, 23, 28 and 31-47 are withdrawn from consideration as being drawn to a non-elected invention.

Priority

Applicant is requested to update the first line of the specification (the continuing data) to include the patent number for 09/314159.

Claims 48-52 have priority to 5/19/98.

Claims 1-2, 4-7, 9, 11-12, 14-17, 19-22, 24-27, 29-30 have priority to 5/22/01 because the parent application only discloses reagents that bind to ATP synthase as angiostatin agonists/antagonists/modulators and does not disclose reagents that bind angiostatin as angiostatin agonist/antagonist/modulator.

Information Disclosure Statement

The IDS filed 6/10/04 and 4/15/03 has been considered and initialed copies of the PTO-1449 are enclosed.

Claim Rejections - 35 USC § 112

Claims 11-12, 14-17, 19-22, 24-27 and 29-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described in In Re Colianni, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in Ex Parte Forman, 230 USPQ 546 (BPAI 1986). Among these factors are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the breath of the claims,
5. the amount of direction or guidance present, and
6. the presence or absence of working examples.

The following is an analysis of these factors in relationship to this application.

Nature of the invention

Applicant discloses and claims the use of any angiostatin agonist/antagonist/modulator, as they read on antibodies and fragments thereof, to either inhibit or promote angiogenesis.

State of the prior art and the predictability or lack thereof in the art

The claimed invention pertains to the highly experimental and unpredictable field of in vivo therapy using monoclonal antibodies. Articles by Waldmann and Harris are cited in order to establish the general state of the art and level of predictability of in vivo human therapy using monoclonal antibodies. The cited references establish that numerous experimental and clinical studies have determined that the effective application of antibody-based therapy methods for in vivo treatment of human diseases has been extremely limited.

Waldmann teaches on page 1657 that, to date, low therapeutic efficacy has been attained in the use of unmodified murine monoclonal antibodies for therapy of human disorders such as cancer and infectious diseases. Harris summarizes recent conferences (Feb. 1993) in the field of therapeutic monoclonal antibodies and teaches that there is widespread acceptance in the art that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy. Harris cites several problems limiting the effective use of rodent monoclonal antibodies including (1) short in vivo half-life; (2) poor recognition of rodent immunoglobulin constant regions with human effector cells and (3) the human immune response (HAMA) against murine proteins. Anti-murine antibodies elicited in the HAMA response complex with administered antibodies and have the effect of rendering repeated antibody dosing ineffective.

The complexity and unpredictability of the art to which the invention pertains provides reasonable basis to question as to the accuracy of applicant's assertion that the antibodies can be used for effective therapy in vivo.

Guidance

There is minimal guidance in the specification as to how to administer the antibodies, the dosages needs, and pharmaceutical formulations acceptable for administration.

Working Examples

Applicant has not presented working examples which would give one skilled in the art a reasonable expectation of using the claimed antibodies to effectively inhibit or promote angiogenesis in vivo. The in vitro data merely shows that polyclonal antibodies directed against either subunit of ATP synthase inhibit enzymatic activity and cell proliferation. There is no evidence that these in vitro assay correlate to in vivo conditions. Thus, this data is insufficient to provide one of skill in the art with a reasonable expectation that the claimed therapeutic composition can be used for in vivo therapy.

Those of skill in the art recognize that in vitro assays are useful to screen the effects of agents on target cells. However, in vivo correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in vitro assay, does not permit a simple extrapolation of in vitro assays to in vivo therapeutic efficacy with any reasonable degree of predictability. In vitro assays depend on cell culture and therefore do not entirely simulate in vivo conditions. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Further, an therapeutic agent must accomplish several tasks to be effective. It must be delivered into the circulation and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In vitro assays cannot duplicate the complex conditions of in vivo therapy. In the assays, the agent is in contact with cells during the entire exposure period. This is not the case in vivo, where exposure at the target site may be delayed or inadequate.

Breadth of the claims

Applicant is claiming broadly. Applicant is claiming that any angiostatin agonist/antagonist/modulator, as they read on antibodies and fragments thereof, can be used to either inhibit or promote angiogenesis. Applicant has only provided examples using polyclonal antibodies directed against the alpha or beta subunit of ATP Synthase. Applicant has not demonstrated that other antibodies (for example, antibodies that bind angiostatin) have similar activities.

In view of the above, it is the Examiner's position that one skilled in the art could not make and/or use the invention without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 48-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Dunn et al J. Biol. Chem Vol. 250 p. 10418 (1985).

This reference discloses monoclonal antibodies that are specific for the alpha or beta subunit of F1-ATPase (see Table II). Absent any objective evidence to the contrary, it is inherent that the monoclonal antibodies function as an angiostatin agonist, angiostatin partial agonist, angiostatin inverse agonist, angiostatin antagonist or angiostatin allosteric modulator.

Claims 1-2 and 4-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Dunn et al J. Biol. Chem Vol. 250 p. 10418 (1985) as evidence by applicant's definitions on pages 11-12 of the specification.

This reference discloses monoclonal antibodies that are specific for the alpha or beta subunit of F1-ATPase (see Table II). On pages 11-12, applicant defines angiostatin agonist, angiostatin partial agonist, angiostatin inverse agonist, angiostatin antagonist or angiostatin allosteric modulator. These are defined as binding to the alpha or beta subunits of F1 ATP synthase. In view of this definition and in view of the disclosure of the references that the monoclonal antibodies bind alpha or beta subunit of F1-ATPase, the reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 and 4-6 and 48-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillman et al US 5786150 as evidence by applicant's definitions on pages 11-12 of the specification.

In col. 7, lines 16-35 and col.16, line 20-col. 18. line 28, this reference discloses ATP Synthase (ASYS) and the use of these antibodies to treat a variety of disorders (which read on angiogeneic disorders).

The only difference between the instant invention and the reference is that reference does not make these antibodies.

However, in view of the explicit suggestion in the reference to make and these antibodies, one of ordinary skill in the art at the time of applicant's invention would immediately envisage the making and use of such antibodies. On pages 11-12, applicant defines angiostatin agonist, angiostatin partial agonist, angiostatin inverse agonist, angiostatin antagonist or angiostatin allosteric modulator. These are defined

as binding to the alpha or beta subunits of ATP synthase. Since the antibodies of the reference bind ATP synthase, absent objective evidence to the contrary, it is expected that these antibodies have these functions.

Claims 1-2 and 4-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman et al 5837682 as evidence by applicant's definitions on pages 11-12 of the specification.

In col. 5, lines 6-24 and col. 21 and col. 24-25 , this reference discloses polyclonal and monoclonal antibodies to angiostatin.

The only difference between the instant invention and the reference is that reference does not make these antibodies.

However, in view of the explicit suggestion in the reference to make these antibodies, one of ordinary skill in the art at the time of applicant's invention would immediately envisage the making of such antibodies. Absent objective evidence to the contrary, it is expected that these antibodies are either agonists or antagonists of angiostatin.

Claims 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillman et al US 5786150 or Folkman et al US 5837682 in view of Allen et al US 6056973.

Hillman and Folkman have been discussed above.

The reference does not teach the antibody conjugated onto a liposome of microparticle.

Allen et al teach the use of lipsome compositons for in vivo administrations for increasing the circulation time of the liposome (see col. 1, lines 15-28).

It would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use the antibodies of Hillman et al or of Folkman in the long-circulating liposome compositions of Allen with the expected benefit of increasing the circulation time.

Claims 1 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillman et al US 5786150 or Folkman et al US 5837682 in view of Masferrer et al US 6025353.

Hillman and Folkman have been discussed above.

The reference does not teach a further composition comprising a COX-2 inhibitor.

Masferrer et al disclose a variety of different COX-2 inhibitors for treating angiogenic disorders.

The MPEP in section 2144.06 states that

> It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) .

In re Kerkhoven it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to combine the antibodies of Hillman et al or of Folkman et al and the compounds of Massferrer et al in order to achieve a composition useful for the same purpose.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J Huff whose telephone number is 571-272-0834. The examiner can normally be reached on Mondays and Thursdays from 5:30am to 2:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheela J Huff
Primary Examiner
Art Unit 1642